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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/593,010

09/18/2006

Susan D. Aster

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EXAMINER

ZAREK, PAUL E

ART UNIT

PAPER NUMBER

1617

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/593,010	<b>Applicant(s)</b> ASTER ET AL.	
	<b>Examiner</b> Paul Zarek	<b>Art Unit</b> 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 December 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 16-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>03/23/2007</u> .  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of the Claims***

1. Claims 1-22 are currently pending. This is the first Office Action on the merits of the claim(s).

### ***Election/Restrictions***

2. Applicant's election without traverse of Group II, drawn to a method of treating a condition responsive to inhibition of 11 $\beta$ -hydroxysteroid dehydrogenase-1, comprising administration of a compound of formula I wherein none of R<sup>3</sup>, R<sup>4</sup>, or R<sup>5</sup> comprise a cyclic group, thus it does not include any heterocyclic ring. The reply filed on 12/16/2008 was not fully correct. Telephone interview with Ms. Heidi Struse on 01/29/2009 (already of record), indicated the election of Group II, without traverse, and the species 4-(5-(2-chlorophenyl)-4-methyl-4H-1,2,4-triazole-3-yl)-1-methyl-1H-indole.
3. Claims 1-15 read on the elected invention. Claims 16-22 were withdrawn as being drawn to a nonelected invention. Examiner notes that the elected species appears to be free of the prior art. The entirety of Claims 1-15 are evaluated on their merits in this office action.

### ***Priority***

4. Applicant's claim for the benefit of a prior-filed international application PCT/US05/009996 (filed on 03/25/2005), which claims the benefit of a prior-filed provisional application 60/557,344 (filed on 03/29/2004) under 35 U.S.C. 119(e) or under 35 U.S.C. 120,

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121, or 365(c) is acknowledged. The effective filing date of the instant application is 03/29/2004.

***Claim Rejections - 35 USC § 112 (1<sup>st</sup> paragraph)***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting 11 $\beta$ -HSD-1 comprising administration of an inhibiting amount of a compound of formula I wherein R<sup>2</sup> is methyl, and R<sup>3</sup>, R<sup>4</sup>, and/or R<sup>5</sup> are:

-H;	C <sub>1</sub> -C <sub>6</sub> alkyl;	C <sub>2</sub> -C <sub>6</sub> alkenyl;	halogen;
OR <sup>7</sup> ;	(CH <sub>2</sub> ) <sub>n</sub> N(R <sup>7</sup> ) <sub>2</sub> ;	cyano;	-NO <sub>2</sub> ;
-CF <sub>3</sub> ;	-CH <sub>2</sub> CF <sub>3</sub> ;	-OCF <sub>3</sub> ;	-OCHCF <sub>2</sub> ; and,
-OCH <sub>2</sub> CF <sub>3</sub> ,			

does not reasonably provide enablement for a method of inhibiting 11 $\beta$ -HSD-1 comprising administration of another compound not listed above, or treating any condition with the compounds of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

7. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” (MPEP § 2164.01(a))

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- a. *The breadth of the claim:* The rejected claims are drawn to a method of treating a condition that is responsive to a therapeutically effective dose of a  $11\beta$ -HSD-1 inhibitor, comprising the administration of a compound of formula I in which  $R^2$  can be a  $C_1$ - $C_8$  alkyl,  $C_2$ - $C_4$  alkynyl, or  $(CH_2)_n$ - $C_3$ - $C_6$  cycloalkyl, and  $R^3$ ,  $R^4$ , and  $R^5$  can be one of a number of substituents that are not obvious variants of each other. Since the claims are drawn to a method of treating, and require a therapeutically effective amount of the compound, the compounds must possess therapeutic activity, *in vivo*;
- b. *Nature of the invention:* The nature of the invention is a method of inhibiting  $11\beta$ -HSD-1 comprising administration of a compound of formula I wherein  $R^2$ ,  $R^3$ ,  $R^4$ , and  $R^5$  are limited to the subgroups listed above;
- c. *The state of the prior art:* The claimed compounds of formula I appear novel and nonobvious over the prior art. Waddell, et al., disclose a triazole derivative comprising a core of the triazole and a substituted phenyl subgroup attached to the triazole on the "east" side. Waddell, et al., differ from the instant application in that the "west" side contains an adamantyl substituent whereas the instant application claims an aryl or heteroaryl substituent. The compounds disclosed by Waddell, et al., are taught to be inhibitors of  $11\beta$ -hydroxysteroid dehydrogenase-1 ( $11\beta$ -HSD-1), and useful for the treatment of a number of diseases associated with non-insulin-dependent diabetes mellitus (NIDDM). Waddell, et al., states only that "[t]he compounds described herein are selective inhibitors of the  $11\beta$ -HSD-1 enzyme" (paragraph 0198). Waddell, et al., disclose no further data indicating that the compounds disclosed therein actually inhibit  $11\beta$ -HSD-1 or can effectively treat any disorder or disease.

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Hermanowksi-Vosatka, et al. (Journal of Experimental Medicine, 2005), teach that 11 $\beta$ -HSD-1 overexpression leads to metabolic-like syndrome in mice, and that 11 $\beta$ -HSD-1 knockout mice are resistant to the development of metabolic syndrome.

Hermanowski-Vosatka, et al., further disclose that at the time of publication, the effect of 11 $\beta$ -HSD-1 inhibition on atherogenesis had not been studied (pg 518, col 1, paragraphs 2 and 3).

Examiner found no reference in the prior art regarding the efficacy of 11 $\beta$ -HSD-1 inhibitors to treat other diseases, such as dementia, retinopathy, etc;

d. *Level of one of ordinary skill in the art:* Medicinal chemists, scientists, and physicians investigating 11 $\beta$ -HSD-1 and diseases/disorders associated with said enzyme would comprise an ordinarily skilled artisan.

e. *Level of predictability in the art:* The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher* (427 F. 2d 833, 166USPQ 18 (CCPA 1970)) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The level of unpredictability in this art is very high. As demonstrated by Aster, et al. (Bioorganic & Medicinal Chemistry Letters, 2008), similar compounds of formula I, wherein R<sup>1</sup> is phenyl or indolyl, and R<sup>2</sup> is methyl display varying pharmacodynamic properties. Tables 1-3 disclose the percent inhibition of [<sup>3</sup>H] cortisone conversion of numerous compounds that are encompassed by the instant claims. Some compounds (i.e. compounds 22, 24, 38, and 39) dramatically inhibit [<sup>3</sup>H] cortisone conversion (% inhibition of greater than 10%) up to 16 hours following administration of the test

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compound. However, some demonstrate almost no inhibition, or even negative inhibition either 4 or 16 hours post administration of the test compound (compounds 4, 5, 25, 33, 36, 40, 43, 48, and 49). The experiments disclosed in Aster, et al., merely demonstrate the ability of the test compounds to inhibit [<sup>3</sup>H] cortisone conversion (presumably through inhibition of 11 $\beta$ -HSD-1), and do not demonstrate or contemplate treating any disorders or diseases that may be amenable to treatment by a 11 $\beta$ -HSD-1 inhibitor. If a compound does not inhibit 11 $\beta$ -HSD-1, then it would be unable to treat a disorder amenable to 11 $\beta$ -HSD-1 inhibition;

f. *Amount of direction provided by the inventor:* Applicants allege that the compounds of the formula I are “selective inhibitors of the 11 $\beta$ -HSD-1 enzyme” (pg 20, paragraph 5, line 1). As 11 $\beta$ -HSD-1 inhibitors, the compounds of formula I inhibit the conversion of cortisone to cortisol, which is associated with numerous disorders (pg 21, paragraph 1, lines 2-9) and “generally have an inhibition constant IC<sub>50</sub> of less than about 500 nM (pg 23, paragraph 3, lines 1-2). Applicants specify a number of diseases and disorders that are potentially amenable to treatment with formula I. The unifying theme behind the listed diseases is the fact that they may comprise an insulin-resistance component;

g. *Existence of working examples:* Applicants provide no working examples of the compounds of formula I inhibiting 11 $\beta$ -HSD-1 or treating any disorder/disease; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure:* Applicant has made only a very small subset of the possible compounds encompassed by the rejected claims. All of the compounds made fall within

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the scope for which the instant application is enabled. Because the instant application is the first time the compounds of formula I have been disclosed, it bears a heavy burden to enable a skilled artisan to make and use the invention as claimed. The instant specification does not provide sufficient guidance to enable one of ordinary skill in the art at the time the invention was made to make all of the huge number of compounds claimed. “Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. . . . [M]ost syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence” (Dorwald, Side Reactions in Organic Synthesis, 2005).

Moreover, Applicant has not provided any data suggesting that any molecule disclosed in the instant application would inhibit 11 $\beta$ -HSD-1, let alone be effective to treat any disease (i.e. Type 2 diabetes). The instant application provides no guidance suggesting that the compounds of formula I would be bioavailable in any therapeutically effective amount. Indeed, Aster, et al., demonstrate the wide variability in the ability of the embodiments of formula I to inhibit cortisone conversion, *in vivo*. Prior to the publication of Aster, et al., in 2008, one of ordinary skill in the art would have had no guidance suggesting which of the claimed compounds of formula I would be active, *in vivo*. Moreover, Aster, et al., only demonstrates *in vivo* activity, specifically, whether the compounds of formula I inhibit 11 $\beta$ -HSD-1. It remains a large leap from *in vivo* activity

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to effectively treating any disease/disorder. There remain a host of pharmacokinetic and therapeutic parameters to be discerned before any of the compounds of formula I could conceivably become a therapeutic agent.

The field of  $11\beta$ -HSD-1 inhibition therapy was in its infancy at the time of filing of the instant application. A search of the prior art found no examples of the claimed  $11\beta$ -HSD-1 to treat any diseases. Seckl and Walker (Endocrinology, 2001), which was cited in the instant application to support treating cognitive disorders and dementia, merely speculate that  $11\beta$ -HSD-1 inhibition *might* reduce cognitive impairment and dementia (pg 1375, col 1, paragraph 1). Seckl and Walker offer no data to support for such a conclusion.

The possible embodiments claimed are not necessarily obvious variants of each other. "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (*Genentech Inc v Nova Nordisk* 42 USPQ 2d 1001). Absent unexpected results, one of ordinary skill could not reasonably determine whether the claimed compounds would be therapeutically efficacious to treat any disease/disorder. The instant specification does not enable one of ordinary skill in the art to make and use the invention commensurate with the scope of the rejected claims. Undue and unpredictable experimentation would be required.

### ***Conclusion***

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7. Claims 1-15 are rejected
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Rita J. Desai/  
Primary Examiner, Art Unit 1625